Response to 'Does postmenopausal hormone therapy influence renal function?'

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We appreciate Dr. Kauffman's interest[1] in our paper.[2] We agree that further exploration of the relationship between timing of hormone therapy (HT) initiation (that is in the perimenopausal vs postmenopausal period) and kidney function would be of great interest. We were limited in our evaluation of the association between HT and change in kidney function to the postmenopausal population, as only residents of Alberta aged $\geqslant$65 years receive complete insurance coverage for prescription drugs. As such, we were only able to ascertain prescriptions filled for this older population. We intentionally limited our study to women with eGFR $<$90 ml/min per 1.73 m^2 to avoid misclassification of kidney function as the original modification of diet in renal disease formula was derived using a population with measured GFR $<$90 ml/min per 1.73 m^2 (ref. 3).

As noted in our study limitations, we were restricted in our assessment of clinical data and thus were not able to comment on menopausal symptomatology in either the control group or the group using HT. However, our study was not designed to assess the appropriateness of prescribing HT or the HT dose, but rather change in kidney function among women who were dispensed HT. Although Dr. Kauffman is correct in pointing out that we could not monitor compliance with the medication, if the women prescribed HT in our study were not actually using this medication regularly, then is it possible the results observed in our study are actually an underestimate of the true effects.

Although the baseline characteristics of study subjects differed by exposure status, our models adjusted for these potential covariates. In addition there was no evidence of confounding or effect modification with angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or non-steroidal antinflammatory drug use, thus these variables were not included in our final models. Although we strongly agree with the suggestion that randomized controlled trials are needed to test the potential benefits or harm of HT on kidney function in both the perimenopausal and postmenopausal woman, the results of our study suggest that surveillance of kidney function in the elderly woman ingesting oral estrogen is warranted.

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Autophagy: a protective mechanism against nephrotoxicant-induced renal injury

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To the Editor: Periyasamy-Thandavan *et al.*[1] demonstrated for the first time a cytoprotective role for autophagy in cisplatin nephrotoxicity. In the accompanying commentary, Lieberthal states that the extent to which autophagy can ameliorate kidney injury caused by other types of renal insults remains to be determined.

We have recently demonstrated that cyclosporine induces autophagy, both *in vitro* in human tubular cells and *in vivo* in rat kidneys, and that autophagy serves as a protective mechanism against cyclosporine toxicity.[2] Importantly, we demonstrated that cyclosporine-induced autophagy is triggered by endoplasmic reticulum (ER) stress. ER stress occurs when excessive amounts of misfolded proteins accumulate inside the ER. Cells subjected to ER stress activate the unfolded protein response to reduce the amount of accumulated proteins. However, persistent ER stress may lead to apoptosis. Recent evidence suggests that ER stress drives autophagy[3] and this self-digestion can rid cells of superfluous or misfolded protein accumulation. Thus, it is suggested that autophagy alleviates the deleterious effects of ER stress by eliminating misfolded proteins. Cisplatin has been shown to induce ER stress.[4] It is therefore tempting to speculate that autophagy induced by cisplatin is also due to ER stress. As ER stress is an emerging pathological process in kidney diseases,[5] autophagy could constitute an adaptive mechanism to kidney injuries far more common than previously thought.

Thus, deciphering new biological pathways that induce autophagy in kidney diseases is of great importance because they may lead to the development of early biomarkers of kidney injury and to new therapeutic options.

1. Periyasamy-Thandavan S, Jiang M, Wei Q *et al.* Autophagy is cytoprotective during cisplatin injury of renal proximal tubular cells. *Kidney Int* 2008; **74**: 631–640.
2. Pallet N, Bouvier N, Legendre C *et al.* Autophagy protects renal tubular cells against cyclosporine toxicity. *Autophagy* 2008; **4**: 783–791.
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Response to 'Autophagy: a protective mechanism against nephrotoxicant-induced renal injury'

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We thank Dr. Pallet and Dr. Anglicheau for their interest in our recent publication reporting autophagy in cisplatin nephrotoxicity and its cytoprotective role.[1] We are pleased to learn that their latest work has also demonstrated autophagy as a protective mechanism against cyclosporine toxicity in renal cells and tissues.[2] Interestingly, whereas we showed the regulation of cisplatin-induced autophagy by p53, BcL-2, and related mechanisms, Pallet *et al.* further emphasized the involvement of ER stress in autophagy during cyclosporine toxicity. Although we did not examine ER stress in the cisplatin model, we believe this is a possibility that deserves consideration and further investigation. As correctly pointed out, cisplatin can induce ER stress. In this regard, Liu and Baliga[3] showed evidence for ER stress during cisplatin treatment of renal tubular cells. Nevertheless, multiple stresses and signaling pathways are induced or activated during cisplatin nephrotoxicity.[4] Notably, cisplatin induces pathological alterations in several subcellular sites or organelles including mitochondria, ER, and the nucleus. As a result, cellular responses, either cytoprotective or injurious, may be mediated by multiple rather than a single mechanism.[4] Certainly, a specific stress or pathway may have a major role in the induction of autophagy; whether it is ER stress remains to be determined. In addition, the signaling pathways activated by cisplatin may also cross talk and be integrated, resulting in an impressive renal pathology. The recent studies by this and other laboratories have suggested that autophagy is a renoprotective mechanism during cisplatin and cyclosporine nephrotoxicity.[1,2,5] However, whether this conclusion can be generalized to other kidney injury models (for example renal ischemia-reperfusion) remains to be investigated, as excessive autophagy can lead to cell death. Thus we have to agree with Dr. Lieberthal that 'the extent to which autophagy can ameliorate kidney injury caused by other types of renal insults remains to be determined'.[6] It is hoped that these studies have provided impetus for investigation of autophagy in renal pathophysiology.

1. Periyasamy-Thandavan S, Jiang M, Wei Q *et al.* Autophagy is cytoprotective during cisplatin injury of renal proximal tubular cells. *Kidney Int* 2008; **74**: 631–640.
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Telmisartan is more effective than losartan in reducing proteinuria

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To the Editor: We read with interest the paper that Telmisartan is more effective than losartan in reducing proteinuria in patients with Diabetic Nephropathy recently published in *Kidney International* by Bakris *et al.*[1] where the effects of telmisartan 80 mg was compared with losartan 100 mg in 860 patients with type 2 diabetes treated for 52 weeks. The authors showed that with telmisartan, proteinuria decreased from 1.42 to 0.95 g per g creatinine ($P<0.0001$) and with losartan, proteinuria decreased from 1.39 to 1.05 g per g creatinine ($P<0.0001$) at the end of the study. They also documented a trend in favor of telmisartan where there was a difference of 4.2 mm Hg difference in systolic blood pressure compared to losartan. We would like to comment on the dose of telmisartan and losartan used in Bakri's study. From our observation, comparing telmisartan 80 mg with losartan 100 mg would favor telmisartan with regards to clinical efficacy in particular with respect to reduction of proteinuria.

We would like to share our own experience in a clinical trial involving patients with IgA nephritis treated with losartan 100 mg ($n=45$) compared to those treated with losartan 200 mg ($n=61$) over a 6-year period from 2001 to 2007.[2] In the losartan 100 mg group, proteinuria decreased from 2.1 ± 1.0 to 1.7 ± 1.0 g/day compared to losartan 200 mg group where proteinuria decreased from 2.1 ± 0.8 to